AUTOMATIC ASSESSMENT OF MYOCARDIAL FIBROSIS BY DELAYED ENHANCED MAGNETIC RESONANCE IMAGING

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ABSTRACT

Cardiovascular magnetic resonance is able to detect myocardial fibrosis by delayed enhancement of a contrast media. However, detection and quantification of fibrosis is difficult due to the complex pattern of the fibrotic tissue signal. In this study a software model of the signal distribution in normal and fibrotic myocardium was inferred from MR images of healthy subjects and patients with hypertrophic cardiomyopathy. The developed model allowed to define a methodology for the discrimination of fibrotic areas. The method was based on the fitting of the signal histogram with a modified gamma function. The scale parameter characterizing the gamma function was used as discriminating factor in MR image analysis, reaching a sensitivity of 85% and a specificity of 86%. The proposed approach outperformed the standard approach used in the clinical practice.

Index Terms—Magnetic resonance imaging, myocardial fibrosis, image processing

1. INTRODUCTION

Delayed enhanced cardiovascular magnetic resonance (DE-CMR) allows to detect myocardial fibrosis, a pathological condition of the myocardial tissue associated with several diseases, as hypertrophic cardiomyophaty (HCM) [1]. In DE-CMR, an inversion recovery gradient echo pulse sequence is used with an inversion time fixed to null signal from normal myocardium. DE-CMR mages are acquired several minutes after the infusion of a paramagnetic contrast media. Because the contrast medium disappears in normal myocardium but it is still present in fibrotic tissue, fibrotic tissue will appear as area with a signal significantly different from zero.

Fibrosis distribution is usually visually assessed by the cardiologist/radiologist calculating the number of left ventricle segments where a significant signal enhancement is present. However, visual detection of these areas is difficult because of the intramyocardial patchy distribution of DE and also because of the presence of myocardial areas mildly enhanced. Hence, the development of computer assisted, quantitative methods for fibrosis detection and quantification is important. Currently, the most used method consists in placing a region of interest (ROI) in the normal myocardium and evaluating a fixed cut-off for delayed enhancement of two standard deviations above the mean signal intensity [2].

Aim of this study was to develop a model of the signal distribution in normal and fibrotic myocardium and propose a methodology for the discrimination of fibrotic area based on the developed model.

2. MATERIALS AND METHODS

2.1. Magnetic Resonance Imaging

Fifteen healthy subjects and 40 patients (30 men) with hypertrophic cardiomyophaty (HCM) were involved in the study. Informed consent was obtained from all subjects. Institutional review board approved the study.

Magnetic resonance examination was performed using a 1.5T whole body scanner (GE Healthcare, Milwaukee, USA). A 4-element (2 anterior and 2 posterior) cardiac phased-array receiver surface coil was utilized for signal reception. Delayed enhancement images were obtained by an inversion recovery gradient echo pulse sequence with an inversion time fixed to null signal from normal myocardium. Images were acquired in the short axis view 8 minutes after contrast media (Gd-DTPA, 0.1 mmol/kg) injection. The following parameters were used: field of view 40 cm, slice thickness 8 mm, no gap between each slice, repetition time 4.6 ms, echo time 1.3 ms, flip angle 20°, acquisition matrix 224 x 192, reconstruction matrix 256 x 256. Depending from left ventricle size, 10 to 14 slices were acquired for each subject. Figure 1 shows two typical DE-CMR images of the myocardium for a normal subject and a HCM patient with diffused fibrosis. As showed in the figure, the presence of fibrosis is associated with an increase of the signal in DE-CMR images due to the deposition of paramagnetic contras medium in fibrotic tissue. All data sets were processed by a Matlab® home-made software, that allows the manual delimitation of the myocardium and the

extraction of pixel values. Signal histogram on the entire myocardium was computed for all 55 subjects. Moreover, the mean signal histogram was calculated for the two populations (i.e. normal and fibrotic subjects).

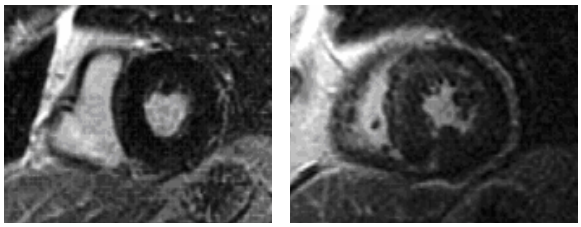

Figure 1: DE-CMR images of normal myocardium (left) and fibrotic myocardium (right).

2.2. Image Model

The DE-CMR technique exploits magnitude MR images where the tissue generated signal in the normal myocardium is imposed to be zero. Hence, the only source of signal in normal myocardium should be Rician distributed noise [3]. In particular, if phased array coils are used, the noise distribution is described by [4]:

$$p(M_n) = \frac{A_n}{\sigma^2}\left(\frac{M_n}{A_n}\right)^n e^{-\left[\left(A_n^2+M_n^2\right)/2\sigma^2\right]} I_{n-1}\left(\frac{M_n \cdot A_n}{\sigma^2}\right) \quad (1)$$

where n is the number of coils (4 in the present study), σ^2 is the variance of noise at each coil receiver, I_{n-1} represents the modified first type Bessel function of order n-1, and A_n is the "true" intensity of the MR signal. When A_n=0 as in the nulled myocardium, the Rician distribution collapses in a Rayleigh distribution, defined by the number of coils n and the noise variance σ^2. The σ value can be estimated from the image background as $\sigma = 1.44\ \sigma_{BK}$ [3,4].

However, measurements on DE-CMR images of the 15 healthy subjects involved in the study revealed that a simple Rician distribution could not fully explain the detected signal distribution. In particular, the Rician distribution did not account for extreme values of the signal in healthy myocardium. This finding matched with the empirical observation that some bright pixels may be randomly present even in the normal myocardium, due to permanence of contrast media and image artefacts. An effective image model should take into account these extreme values, because they are important in the assessment of fibrosis.

Hence, the image model was built by a Montecarlo algorithm in the following way:

1. A circular crown resembling the myocardium as seen in DE-CMR short axis planes was built;
2. k pixels were randomly drawn on the model. Pixel signal values were randomly generated from a Gaussian distribution $G_1(m_1, \sigma_1)$.
3. q pixels were randomly drawn on the model. Pixel signal values were randomly generated from a Gaussian distribution $G_2(m_2, \sigma_2)$.
4. Rician distributed noise was added as described in Eq. 1. The σ value that characterizes the noise distribution was inferred from background of DE-CMR images used in the study.

TABLE I
OPTIMIZED PARAMETERS OF THE IMAGE MODEL

Parameter	Healthy myocardium	Fibrotic myocardium
k	21 %	25.2%
m_1	14.8	19.0
σ_1	2.01	1.9
q	0.3 %	1.0%
m_2	14.8	45.7
σ_2	2.12	3.1

The model is characterized by six unknown parameters (k, q, m_1, σ_1, m_2, σ_2). The parameters values were tuned by minimizing the mean square difference between the myocardial signal histogram evaluated on DE-CMR images of the studied subjects and the signal histogram generated by the model. 100 model realizations were used by using the Nelder-Mead Simplex Direct Search algorithm for model optimization. Table 1 shows the values of the optimized parameters. As showed in the table, signal distribution in healthy myocardium is explained by one Gaussian source, extended on about 20% of the myocardial tissue. This region is slightly larger in fibrotic myocardium.

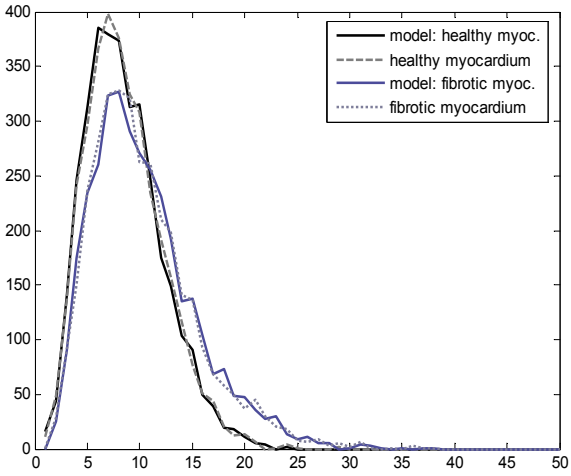

Figure 2: Signal histograms generated by the image model and extracted from DE-CMR images for healthy and fibrotic

myocardium.

A second Gaussian source, with significantly larger mean signal intensity, it is needed to match the signal distribution in DE-CMR images of HCM patients. Figure 2 depicts the mean signal distributions generated by the model and measured on real DE-CMR data.

2.3. Fibrosis detection

Observation of figure 2 suggests that threshold based methods, as the ones commonly used in literature, could not capture the complexity of the signal distribution in fibrotic myocardium. This qualitative finding is confirmed by the experiments performed on the developed model. In particular, 640 model realizations (320 normal, 320 fibrotic) were generated. For each realization, the obtained signal distribution histogram was fitted by several signal distribution models (Gaussian, Rician, Rayleigh, modified Gamma, chi-square, non central chi-square). For each fitting operation, the root mean square error (RMSE) was computed. As showed in table 2, we found that the distribution that realizes the best fitting of the signal distribution in both healthy and fibrotic myocardium is the modified gamma function:

$$G(x) = k\left(x - dx\right)^{b} e^{-\frac{(x-dx)}{c}} \qquad (2)$$

where the distribution is characterized by the b and c factors, namely shape factor and scale factor, respectively. The parameters k and dx allow multiplying and shifting the distribution.

In the same experiment, the effectiveness of the four parameters that characterize the tested function in discriminating between normal and fibrotic tissue was measured. Statistical significance of the difference of parameters means evaluated on normal and pathological model realization was assessed by unpaired T-test. Difference was significant for both shape factor and scale factor ($p<0.001$). Receiver operator curves (ROC) were computed for both parameters, revealing that the scale factor c is the most effective in discriminating between normal and fibrotic myocardium. Figure 3 shows the ROC curve evaluated on model realizations. The optimal threshold was 2.48 with sensivity of 84% and specificity of 86%.

Hence, the discrimination between normal and fibrotic tissue was implemented as follows:

1. The signal histogram is computed from a ROI defined in the myocardium;
2. the histogram is fitted by the modified gamma function by the Levenberg-Marquadt algorithm [5];
3. the parameter c from Eq. 2, evaluated in the curve fitting operation is compared with a given threshold, that discriminates between normal and fibrotic tissue.

TABLE II
COMPARISON OF SIGNAL DISTRIBUTION MODELS

Model	RMSE normal myocardium	RMSE Fibrotic myocardium
Gaussian	129	145
Rician	72	71
Rayleigh	51	68
Modified Gamma	49	49
Chi-square	57	58
Non-central χ^2	57	49

3. RESULTS

The developed method was tested on the real DE-CMR data acquired in the study and the results were compared with the standard methodology. DE-CMR images were processed with home-made software as previously described. The same operator performed the analysis with the two methods. For each subject, the standard deviation (SD) based method required the manual tracing of a ROI on all short axis slices in a myocardial region defined as normal by the operator. Mean and SD of signal inside ROIs were evaluated.

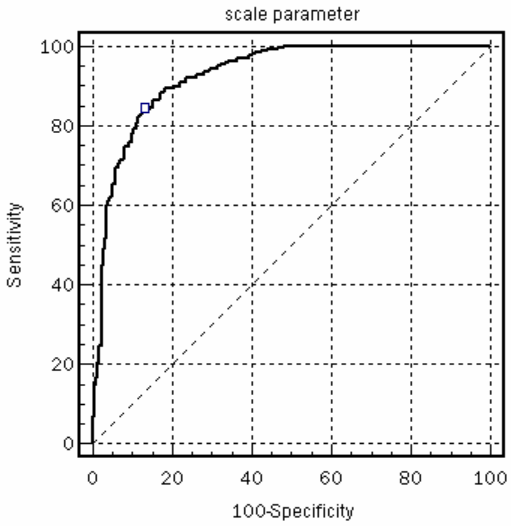

Figure 3: ROC curve evaluated on the image model for the scale parameter *c*. The optimal threshold was 2.48 with sensivity of 84% and specificity of 86%.

A signal threshold T_{SD} was defined as mean+2SD. The operator also manually drew the endocardial and epicardial contours on all images. Signal values inside the entire

myocardium were extracted. The percentage of fibrotic pixels was defined as the number of pixels with a signal value greater than the threshold T_{SD}.

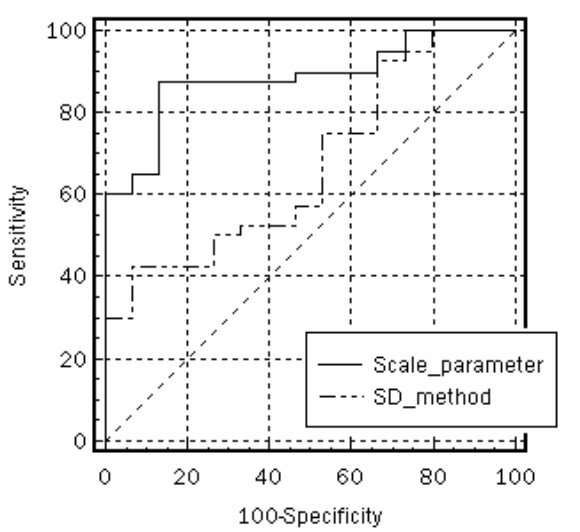

Figure 4. ROC curves evaluated on DE-CMR images for the SD-based and the automatic method.

This percentage was used as discriminating factor in fibrosis assessment by the SD-based method. Histogram of the myocardial signal values was computed and fitted with the modified gamma function (Eq. 2). The scale factor computed in the fitting process was used as discriminating factor in the automatic method.

Figure 4 shows the ROC curves related to the analysis of the 55 subjects involved in the study. For the SD-based method, the optimal threshold was 28.8% with a sensitivity of 42% and a specificity of 93%. The ROC computed for the automatic method was similar to the one computed on the model (see Figure 3), leading to a sensitivity of 85% and a specificity of 86% at the optimal threshold.

4. DISCUSSION

MR signal distribution in DE-CMR images is complicated by the effect of several factors, as non-gaussian noise, imperfect nulling and residual effect of contrast media in normal myocardium, and image artefacts. Hence, standard approaches based on the computing of normal signal values from first order signal statistics could be not adequate, as showed in figure 4.

In this study we propose a different approach, based on the computing of the image histogram and the fitting with an appropriate model. The optimal model was defined by a simulation performed on a software image model inferred from real DE-CMR images. The proposed model was able to effectively discriminate between normal and fibrotic myocardium, outperforming the standard, threshold-based methodology. In the present study, validation was performed on the same data set used for the method developing. Tests on a different patients population should be carried out to fully assess the clinical significance of the proposed approach.

The method appears also suitable for developing segmental analysis of the left ventricle. In segmental analysis short axis slices are automatically segmented in a number of radial sectors in order to build a standardized model [6]. This approach was effectively implemented on DE-CMR images for evaluation of myocardial viability [7] and could be extended to myocardial fibrosis studies.

5. REFERENCES

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